An animal model of attention deficit hyperactivity disorder

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Attention deficit hyperactivity disorder (ADHD) is a common condition that affects a significant percentage of the school-aged and adult population. The core symptoms of this disorder include, but are not limited to, impulsivity, hyperactivity and inattention[1]. The causes and pathophysiology of ADHD are unknown, but compelling evidence suggests an involvement of both genetic and non-genetic factors. The neurotransmitter dopamine (DA) is believed to play a critical role in the generation of symptoms of ADHD, but norepinephrine and serotonin neurotransmission might also contribute to the pathogenesis of this disorder. The most commonly used pharmacotherapy for ADHD is based on the paradoxical ability of psychostimulants [for example, methylphenidate (Ritalin) and amphetamine] to produce an ameliorating (calming) effect in subjects with this condition.

The plasma-membrane dopamine-transporter (DAT) is responsible for recapturing extraneuronal DA, thereby providing tight spatial and temporal control over the intensity of central DA signaling. Psychostimulants exert their action primarily through inhibition or reversal of DAT function, and the resultant increase of dopaminergic transmission in the basal ganglia is believed to underlie behavioral activation and hyperactivity[4]. Recently, a positive association of a polymorphism in the dopamine transporter (DAT) gene with ADHD has been reported by Cook *et al.*[2], and this finding has been replicated by at least two other groups. In our study, mice with a genetic deletion of DAT (DAT-knockout mice, DAT-KO) demonstrate several key characteristic features of ADHD, such as hyperactivity, cognitive impairment (particularly a deficit in inhibitory control of behavior) and paradoxical calming responses to psychostimulants[4]. Moreover, it was shown that the calming effect of psychostimulants in this mouse model is mediated through enhancement of serotonergic transmission. This is presumably achieved via the interaction of the psychostimulants with the serotonin transporter (another known, but largely ignored, target of psychostimulants).

Although the novelty-driven hyperactivity phenotype, the impairment of cognitive functions and the paradoxical calming effects of psychostimulants strongly suggest that DAT-KO mice have properties reminiscent of ADHD, there are obvious caveats. First, it should be noted that it is unlikely that complete functional absence of DAT occurs in ADHD patients and, consequently, DAT-KO mice represent an extreme case of a potential DAT dysfunction. Second, ADHD, if genetically determined, is most likely to result from the malfunction of several genes, and DAT-KO mice illustrate only one potential cause. Third, the calming effect of Ritalin, the most commonly used therapy for ADHD, requires substantially higher doses in DAT-KO mice than in humans, but this might be the result of pharmacokinetic differences between mice and humans because amphetamine (Dexedrine) is effective in the same dose range in both species. Moreover, the same calming effect of psychostimulants in DAT-KO mice has not yet been corroborated by determination of improvement in cognitive performance (particularly attention) in these mice. Such observations are required to further strengthen the validity of DAT-KO mice as a resource to test potential pharmacotherapies for ADHD. Finally, although it is clear that agents that selectively raise serotonin levels are effective calming agents in DAT-KO mice, serotonergic drugs have been of limited use for ADHD in humans and further controlled clinical studies are warranted.

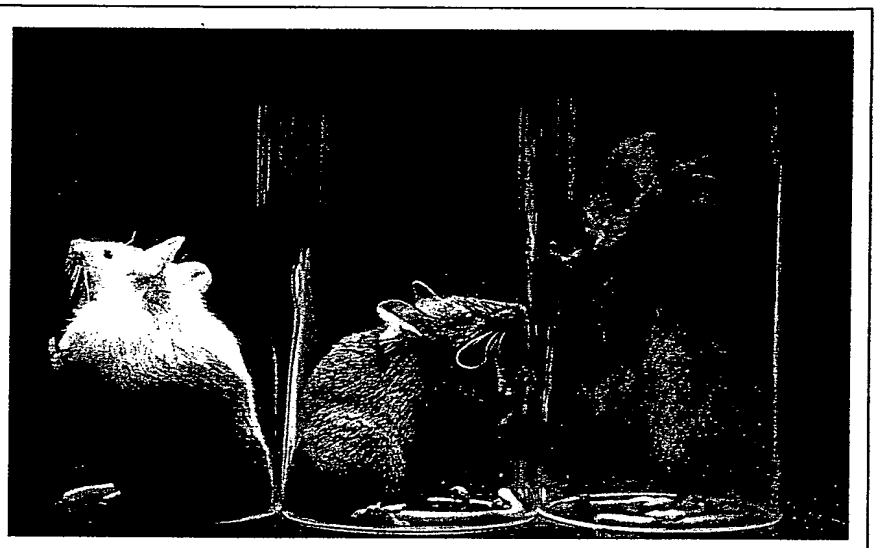

Figure 1. Hyperactivity of the DAT-KO mice (right) in comparison to heterozygous (center) and wild-type (left) littermates. The time-lapse photography is reproduced from Ref. 6.

ADHD is considered to be a developmental disorder that displays a significant reduction in the number of affected individuals with increasing age[1]. These observations might indicate that, during the course of the disorder, susceptibility to pathological manifestations and therapeutic responses could vary. It is worth mentioning that DAT and the serotonin transporter follow divergent patterns of expression in various brain areas throughout postnatal development[3,5], and altered responses to psychostimulants in different age groups, even in normal subjects, might be expected. It is reasonable to hypothesize

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Table 1. The suitability of mice lacking the dopamine transporter as a potential model of ADHD[a]

Similarities to human disease	Differences from human disease	Additional remarks
Environment-dependent hyperactivity	Evidence of DAT malfunction in humans is still elusive	The DAT-KO mouse model raises the possibility that a developmental or genetic imbalance between serotonin and dopamine systems (such as in the functional states of the DAT and serotonin transporter) could determine hyperkinetic behaviors and responses to psychostimulants in humans
Cognitive impairment[b]		
Calming effect of psychostimulants	Different dose range of Ritalin for calming effect	
Similar dose range of Amphetamine for calming effect	Serotonergic agents mimic psychostimulant effects in DAT-KO mice whereas therapeutic efficacy of selective serotonergic drugs in humans with ADHD is not commonly recognized	

[a]Abbreviations: ADHD, attention deficit hyperactivity disorder; DAT, plasma-membrane dopamine-transporter; DAT-KO, DAT-knockout. [b]As shown primarily by perseverative behavior in the 8-arm radial maze.

that both genetically and developmentally determined malfunction of DAT (and/or abnormalities in other neurotransmitter systems) could significantly contribute to the hyperactivity phenotype.

In summary, DAT-KO mice exhibit several characteristic features of the symptoms of ADHD in humans and might provide a valuable animal model for this disorder. By studying the hyperactivity of DAT-KO mice, it might be possible to clarify the neuronal circuitry and specific receptor subtype(s), primarily responsible for hyperkinetic behavior. In addition, the calming effects of psychostimulants in these mice could be investigated, thus furthering our understanding of the underlying deficits in humans with ADHD.

References

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